Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)

Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, Aupérin A, Le Chevalier T, Stephens RJ, Arriagada R, Higgins JPT, Johnson DH, Van Meerbeeck J, Parmar MKB, Souhami RL, Bergman B, Douillard JY, Dunant A, Endo C, Girling D, Kato H, Keller SM, Kimura H, Knuuttila A, Kodama K, Komaki R, Kris MG, Lad T, Mineo T, Piantadosi S, Rosell R, Scagliotti G, Seymour LK, Shepherd FA, Sylvester R, Tada H, Tanaka F, Torri V, Waller D, Liang Y, for the Non-Small Cell Lung Cancer Collaborative Group

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[Intervention Review]

Adjuvant chemotherapy for resected early-stage non-small cell lung cancer

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ABSTRACT

Background

To evaluate the effects of administering chemotherapy following surgery, or following surgery plus radiotherapy (known as adjuvant chemotherapy) in patients with early stage non-small cell lung cancer (NSCLC),we performed two systematic reviews and meta-analyses of all randomised controlled trials using individual participant data. Results were first published in The Lancet in 2010.

Objectives

To compare, in terms of overall survival, time to locoregional recurrence, time to distant recurrence and recurrence-free survival:

A. Surgery versus surgery plus adjuvant chemotherapy

B. Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy

in patients with histologically diagnosed early stage NSCLC.

(2)To investigate whether or not predefined patient subgroups benefit more or less from cisplatin-based chemotherapy in terms of survival.

Search methods

We supplemented MEDLINE and CANCERLIT searches (1995 to December 2013) with information from trial registers, hand-searching relevant meeting proceedings and by discussion with trialists and organisations.

Selection criteria

We included trials of a) surgery versus surgery plus adjuvant chemotherapy; and b) surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy, provided that they randomised NSCLC patients using a method which precluded prior knowledge of treatment assignment.

Data collection and analysis

We carried out a quantitative meta-analysis using updated information from individual participants from all randomised trials. Data from all patients were sought from those responsible for the trial. We obtained updated individual participant data (IPD) on survival, and date of last follow-up, as well as details of treatment allocated, date of randomisation, age, sex, histological cell type, stage, and performance status. To avoid potential bias, we requested information for all randomised patients, including those excluded from the investigators' original analyses. We conducted all analyses on intention-to-treat on the endpoint of survival. For trials using cisplatin-based regimens, we carried out subgroup analyses by age, sex, histological cell type, tumour stage, and performance status.

Main results

We identified 35 trials evaluating surgery plus adjuvant chemotherapy versus surgery alone. IPD were available for 26 of these trials and our analyses are based on 8447 participants (3323 deaths) in 34 trial comparisons. There was clear evidence of a benefit of adding chemotherapy after surgery (hazard ratio (HR)= 0.86, 95% confidence interval (CI)= 0.81 to 0.92, p< 0.0001), with an absolute increase in survival of 4% at five years.

We identified 15 trials evaluating surgery plus radiotherapy plus chemotherapy versus surgery plus radiotherapy alone. IPD were available for 12 of these trials and our analyses are based on 2660 participants (1909 deaths) in 13 trial comparisons. There was also evidence of a benefit of adding chemotherapy to surgery plus radiotherapy (HR= 0.88, 95% CI= 0.81 to 0.97, p= 0.009). This represents an absolute improvement in survival of 4% at five years.

For both meta-analyses, we found similar benefits for recurrence outcomes and there was little variation in effect according to the type of chemotherapy, other trial characteristics or patient subgroup.

We did not undertake analysis of the effects of adjuvant chemotherapy on quality of life and adverse events. Quality of life information was not routinely collected during the trials, but where toxicity was assessed and mentioned in the publications, it was thought to be manageable. We considered the risk of bias in the included trials to be low.

Authors' conclusions

Results from 47 trial comparisons and 11,107 patients demonstrate the clear benefit of adjuvant chemotherapy for these patients, irrespective of whether chemotherapy was given in addition to surgery or surgery plus radiotherapy. This is the most up-to-date and complete systematic review and individual participant data (IPD) meta-analysis that has been carried out.

PLAIN LANGUAGE SUMMARY

Chemotherapy after surgery for early stage non-small cell lung cancer

Review question

Do patients with non-small cell lung cancer live longer if they are given chemotherapy after surgery?

Background

Non-small cell lung cancer is the most common type of lung cancer. If the tumour is early stage, not too big and has not spread to other parts of the body, doctors usually operate to remove it. At the same time, they will also remove a bit of the lung, or the entire lung that has the tumour. They may also give radiotherapy (treatment with x-rays) after the operation, aiming to kill any remaining cancer cells. They may also give chemotherapy (drug treatment) after surgery to lower the risk of the cancer coming back. This treatment is called adjuvant chemotherapy.

In 1995, we did a systematic review and meta-analysis of individual participant data looking at adjuvant chemotherapy and surgery (with or without radiotherapy). It brought together information from all patients who took part in similar trials. These trials compared what happened to people with non-small cell lung cancer who were given chemotherapy after surgery (with or without radiotherapy) with those who had surgery without chemotherapy (with or without radiotherapy). We found that it was not clear whether chemotherapy helped patients with non-small cell lung cancer live longer.

Since this study was completed, many new trials have been done. Therefore, we carried out a new systematic review and meta-analysis of individual participant data that included all trials, old and new. This study aimed to find out if giving chemotherapy after surgery (with or without radiotherapy) can a) help patients live longer, b) stop the cancer coming back (recurrence), and c) stop the cancer spreading to other parts of the body (metastases).

We carried out two studies called meta-analyses that included patients with non-small cell lung cancer that took part in randomised controlled trials comparing:

a) surgery versus surgery plus adjuvant chemotherapy; and

b) surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy.

Results were first published in the Lancet in 2010.

Study characteristics

We searched for relevant trials up to December 2013. The studies brought together trial data from all over the world with 26 trials (34 trial comparisons) and 8447 patients in the first meta-analysis (surgery versus surgery plus adjuvant chemotherapy); and 12 trials (13 trial comparisons) and 2660 patients in the second meta-analysis (surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy). Trials were carried out between 1979 and 2003.

Key results

Results found that people with non-small cell lung cancer that had surgery followed by chemotherapy (with or without radiotherapy), lived longer than those who had surgery without chemotherapy (with or without radiotherapy).

After five years, 64 out of every 100 patients who were given chemotherapy after surgery were alive compared to 60 patients out of every 100 who just had surgery. For those who also received radiotherapy, after five years, 33 out of every 100 patients who received chemotherapy, surgery and radiotherapy were alive compared to 29 out of every 100 patients who received surgery and radiotherapy.

Quality of life information was not routinely collected during the trials, but where toxicity was assessed and mentioned in the publications, it was thought to be manageable.

In both studies, there was little variation in the effect of chemotherapy according to the type of chemotherapy given, other trial characteristics, or by the type of patient included in the trial.

Quality of evidence

These systematic reviews and meta-analyses use individual participant data, which is considered the gold standard of this type of review. We included all eligible trials if possible, no matter what language they were published in or whether they were published or not. The first meta-analysis (surgery versus surgery plus adjuvant chemotherapy) included 92% of all patients in eligible trials and the second meta-analysis (surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy) included 86% of all patients in eligible trials.

We are confident that further research is unlikely to change the findings. The studies were well designed and conducted, address the review question, and the effects are consistent across trials. The impact of any data we have not been able to include in our analyses is small.

BACKGROUND

Description of the condition

Worldwide, around 1.5 million new cases of lung cancer are diagnosed annually (Parkin 2005), and approximately 85% of such cases are non-small cell lung cancer (NSCLC).(American Cancer Society 2007). Although surgery is regarded as optimal treatment, only 20% to 25% of tumours are suitable for potentially curative resection (Datta 2003), therefore other treatments are also used. Our previous individual participant data (IPD) meta-analyses (NSCLC Collaborative Group 1995), gave evidence that cisplatin-based chemotherapy after surgery might prolong survival (hazard ratio (HR)] = 0.87, 95% confidence interval (CI)= 0.74 to 1.02, p= 0.08). With fewer trials and patients, the value of chemotherapy following surgery plus postoperative radiotherapy was less clear (NSCLC Collaborative Group 1995). Recent meta-analyses (Berghmans 2005; Bria 2005; Hamada 2005; Hotta 2004; Pignon 2008; Sedrakyan 2004) showing significant survival benefits with adjuvant chemotherapy, that is chemotherapy given after surgery, have included a variety of trials and patients (Table 1).

Description of the intervention

This review concentrated on randomised controlled trials that had tested surgery alone with drug treatment (chemotherapy) with or with out radiotherapy after surgery. These trials mainly used cisplatin-based chemotherapy, this is commonly used for treatment of lung cancer as well as other cancers. Some trials, mainly those that took place in Asia, used UFT (also called tegafur/uracil) chemotherapy.

How the intervention might work

If the tumour is early stage, for example, not too big and has not spread to other parts of the body, doctors usually operate to remove it. At the same time, they will also remove a bit of the lung, or the entire lung that has the tumour. They may also give radiotherapy after the operation, aiming to kill any remaining cancer cells. They may also give chemotherapy after surgery to lower the risk of the cancer coming back. This treatment is called adjuvant chemotherapy.

Why it is important to do this review

The aim of this review was to assess more reliably the effects of adjuvant chemotherapy, with or without postoperative radiotherapy, in two new comprehensive IPD meta-analyses. Contrary to our previous meta-analyses, the present study is restricted to patients with early stage disease.
Results of these two meta-analyses were first published in The Lancet in 2010 (NSCLC Meta-analysis Collaborative Group 2010).

OBJECTIVES

To compare, in terms of overall survival, time to locoregional recurrence, time to distant recurrence and recurrence-free survival:

A. Surgery versus surgery plus adjuvant chemotherapy

B. Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy

in patients with histologically diagnosed early stage non-small cell lung cancer.

(2)To investigate whether or not predefined patient subgroups benefit more or less from cisplatin-based chemotherapy in terms of survival.

Part A was carried out by the MRC CTU at UCL in London, UK and Part B was carried out by the Institute Gustave Roussy, Villejuif, France.

METHODS

Criteria for considering studies for this review

Types of studies

To be included, both published and unpublished completed trials had to be properly randomised using established methods (not quasi-randomised). Trials could not have been confounded by additional therapeutic differences between the two arms and must have commenced randomisation on or after 1 January 1965. Trials should have aimed to include patients who had undergone a potentially curative resection and not received previous chemotherapy. For the first meta-analysis, trials should have compared surgery versus surgery plus adjuvant chemotherapy. For the second, trials should have compared surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy. We excluded trials using long-term alkylating agents for more than a year because these are no longer used to treat non-small cell lung cancer (NSCLC), and have been shown to be harmful (NSCLC Collaborative Group 1995).

Types of participants

Eligible trials included individuals with histologically confirmed NSCLC who had undergone a potentially curative resection. We included individual participant data from all randomised patients in the meta-analyses, and where possible obtained data for individuals who had been excluded from the original trial analyses. We excluded from the meta-analyses patients with small cell lung cancer that were included in early trials that randomised all types of lung cancer.

Types of interventions

We classified trials as belonging to one of the following categories of chemotherapy.

- Surgery versus surgery plus adjuvant chemotherapy
  - platinum plus vinca alkaloid/etoposide
  - platinum plus vinorelbine
  - platinum plus taxane
  - other platinum regimens
  - platinum plus vinca alkaloid plus tegafur and uracil/tegafur
  - tegafur and uracil/tegafur plus other agent
  - tegafur and uracil/tegafur
- Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy
  - platinum plus vinca alkaloid/etoposide
  - platinum plus vinorelbine
  - other platinum regimens
  - antimetabolic agent only

Types of outcome measures

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Primary outcomes

The primary outcome was overall survival, defined as the time from randomisation until death by any cause. Living patients were censored on the date of last follow-up

Secondary outcomes

Recurrence-free survival was defined as the time from randomisation until first recurrence, or death by any cause. Patients alive without disease were censored on the date of last follow-up. To avoid bias from under-reporting of subsequent events, time to locoregional recurrence was defined as the time from randomisation until first locoregional recurrence, with patients experiencing earlier distant recurrences being censored at the time of distant recurrence. Similarly, for time to distant recurrence, patients experiencing earlier locoregional recurrences were censored on that date. Patients who died without recurrence were censored on date of death. Data on quality of life and adverse events were not routinely collected in the trials and therefore could not be analysed in this review.

Search methods for identification of studies

To limit publication bias, we included published and unpublished trials with no restriction based on language. We carried out searches of MEDLINE and CANCERLIT from 1995 (using The Cochrane Collaboration's optimal strategy (Lefebvre 2001; Lefebvre 2008).We supplemented trial registers by handsearches of conference proceedings and reference lists of trial publications and review articles. We asked our collaborators if they knew of additional trials. We carried out initial searches in 2003 and regularly updated these; we carried out the most recent searches in December 2013.

Electronic searches

We modified The Cochrane Collaboration's optimum search strategy for retrieving randomised controlled trials (RCTs) from MEDLINE (Appendix 1) to specifically retrieve RCTs of chemotherapy for NSCLC and used this search strategy to search MEDLINE and CANCERLIT (1995 to 2013).
In addition, we searched the following electronic bibliographic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (1995 to 2013)
- Proceedings of American Society for Clinical Oncology (ASCO) (1995 to 2013)

We used the following trial registers to supplement searches of electronic databases with trials that were not (yet) published or were still recruiting patients.

- United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Trials Register
- ClinicalTrials.gov
- Physicians Data Query Protocols (open and closed)
- Current Controlled Trials 'metaRegister' of controlled trials

Searching other resources

Handsearches

We carried out the following handsearches to identify trials that may have only been reported as abstracts or that might have been missed in the searches described above.

- Proceedings of the American Society for Clinical Oncology (ASCO) 1993 to 1994
- Proceedings of the International Association for the Study of Lung Cancer (IASLC) World Lung Cancer Conference 1997 to 2013
- Proceedings of the European Society of Medical Oncology (ESMO) 1996 to 2013
- Proceedings of the European Cancer Conference Organization (ECCO) 1995 to 2013

Reference lists

We searched bibliographies of all identified trials and review articles.

Correspondence

We asked all participating trialists to review and supplement a provisional list of trials.

Data collection and analysis

Selection of studies

Four Members of the Project Management Group (SB, AA, JPP, LA) checked all titles and abstracts, identified by both electronic searching and handsearching of conference proceedings, and obtained the full publications for those thought to be potentially relevant. We sought individual participant data (IPD) from trial authors, including updated follow-up, where available.

Data extraction and management

We sought individual participant data for all eligible trials. For the 15 trials originally included in the 1995 analysis of the NSCLC Collaborative Group, we only sought updated follow-up. For new trials, we sought data on age, sex, extent of resection, pathological tumour stage, histology, performance status, treatment arm, date of randomisation, recurrence, survival and follow-up for all patients randomised.
We used standard checks to identify missing data. We verified the data, for example, by checking the order of the dates, and assessed data validity and consistency. To assess randomisation integrity, we checked patterns of treatment allocation and balance of baseline characteristics by treatment arm. We checked follow-up of surviving patients to ensure that it was balanced by treatment arm and up-to-date. We resolved any queries and each trial investigator or statistician verified the final database.

Project co-ordination

Two teams co-ordinated the project management. Each team collected and checked data and analysed results for their comparison as follows:

- Team A: surgery versus surgery plus adjuvant chemotherapy (MRC CTU at UCL, London, UK);
- Team B: surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy (Institut Gustave Roussy, Villejuif, France).

Assessment of risk of bias in included studies

We assessed the included studies using The Cochrane Collaboration's 'Risk of bias' tool outlined in Table 8.5c of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and these studies were checked by a second review author. We considered adequate sequence generation and allocation concealment to be most important and therefore a judgement of low risk was desirable for these domains for all trials. Blinding was not appropriate due to the nature of the treatments and any issues surrounding the reporting of incomplete outcome data, selective

outcome reporting or attrition bias were overcome by the collection of IPD.

Measures of treatment effect

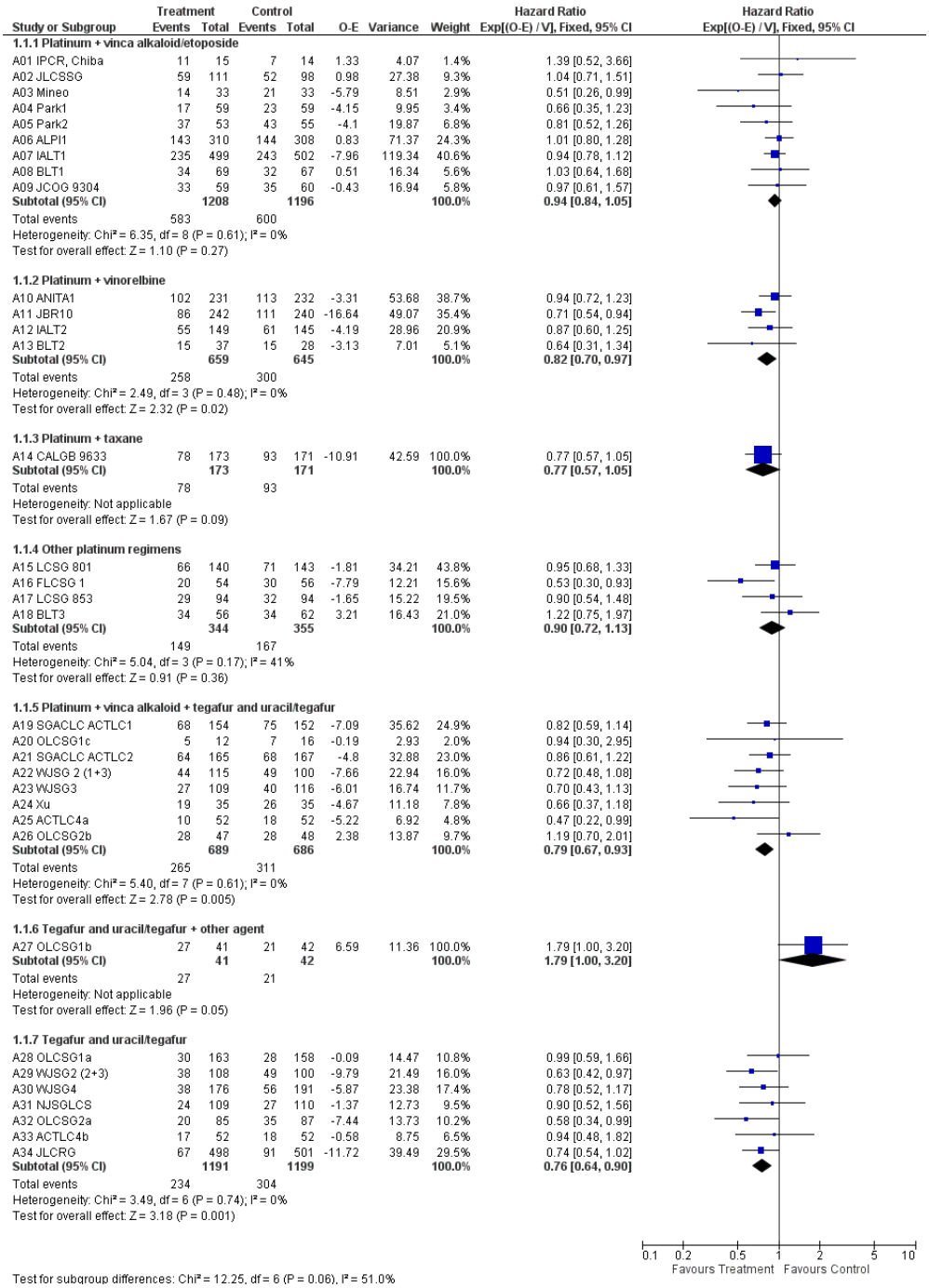
Unless otherwise stated, we prespecified all analyses in the protocols, and carried out on an intention-to-treat analysis. For each outcome, we used the logrank expected number of events and variance to calculate individual trial hazard ratios (HRs), which were pooled across trials using the fixed-effect model. We presented overall survival using simple (non-stratified) Kaplan-Meier curves. We computed the median follow-up for all patients using the reverse Kaplan-Meier method (Schemper 1996).

To explore any impact of trial characteristics on the effect of adjuvant chemotherapy on overall survival, we calculated pooled HRs for each prespecified trial group and used Chi^2 tests for interaction to investigate differences in the treatment effect across these trial groups.

We calculated absolute differences in overall survival at five years using overall HRs and control group survival. If we identified a difference in effect by trial group or patient subgroup, we used HRs and control group survival for the relevant groups to calculate absolute differences; otherwise we used the overall HR.

As two trials compared two adjuvant chemotherapy regimens with one control arm, we compared each treatment arm with the control arm and analysed these as separate trial comparisons in different chemotherapy categories (A22 WJSG 2 (1+3); A25 ACTLC4a; A29 WJSG2 (2+3); A33 ACTLC4b). To avoid double-counting the control arms in the overall and subgroup analyses, however, we combined the treatment arms and compared them with the relevant control arm. Because of this, there are no overall totals in Figure 1. For other trials that belonged in different chemotherapy categories (A06 ALPI1; B06 ALPI2), different meta-analyses or both (A07 IALT1; A08 BLT1; A12 IALT2; A13 BLT2; A18 BLT3; A20 OLCSG1c; A27 OLCSG1b; A28 OLCSG1a; B07 IALT3; B08 BLT4; B10 IALT4; B13 OLCSG1d) we compared relevant patients from the treatment arm with the corresponding control arm patients, and analysed them as separate trial comparisons. This gives a greater number of trial comparisons than there are trials.

Figure 1. For all chemotherapy groups, HR 0.86 (0.81 to 92); p< 0.0001Forest plot of comparison: 1 surgery versus surgery + chemotherapy, outcome: 1.1 survival.



Dealing with missing data

We outlined all desired variables in a protocol (available on request from SB). We requested any missing variables from those who carried out the trial.

Assessment of heterogeneity

We used Chi^2 tests and the I^2 statistic to test for differences in the treatment effect across groups of trials or groups of patients.

Assessment of reporting biases

As we collected IPD, we did not encounter any reporting biases.

Data synthesis

Where we could get data, we included all eligible trials in the analyses. The analyses were carried out in RevMan (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

To investigate differences in the treatment effect across patient subgroups, we undertook Cox regressions, including the relevant treatment by subgroup interaction term within trials and the interaction coefficients (HRs) pooled across trials (Fisher 2011). We investigated whether there were differences in the treatment effect depending upon the patients' age, sex, histological cell type, tumour stage, or performance status.

Sensitivity analysis

We outlined in the protocol that HRs for overall survival would be calculated, excluding any trials that were clear outliers.

RESULTS

Description of studies

Surgery versus surgery plus adjuvant chemotherapy

We identified 35 eligible trials. We included 26 trials; nine from the 1995 meta-analysis and 17 additional ones (see Characteristics of included studies). We could not include nine trials because data were not available for three published (Ayoub 1991; Clerici 1991; Ichinose 1991) and two unpublished trials (EORTC 08922; NCCTG 852451) (see Characteristics of excluded studies); adequate contact with the investigators could not be established for two trials (Ueda 2004; Zarogoulidis 1996) and two other trials had only recently been presented (Wang 2009; Wu 2009). Therefore, we included data from 26 published trials, allowing 34 trial comparisons (A01 IPCR, Chiba; A02 JLCSSG; A03 Mineo; A04 Park1; A05 Park2; A06 ALPI1; A07 IALT1; A08 BLT1; A09 JCOG 9304; A10 ANITA1; A11 JBR10; A12 IALT2; A13 BLT2; A14 CALGB 9633; A15 LCSG 801; A16 FLCSG 1; A17 LCSG 853; A18 BLT3; A19 SGACLC ACTLC1; A20 OLCSG1c; A21 SGACLC ACTLC2; A22 WJSG 2 (1+3); A23 WJSG3; A24 Xu; A25 ACTLC4a; A26 OLCSG2b; A27 OLCSG1b; A28 OLCSG1a; A29 WJSG2 (2+3); A30 WJSG4; A31 NJSGLCS; A32 OLCSG2a; A33 ACTLC4b; A34 JLCRG).

Platinum-based chemotherapy, without tegafur plus uracil or tegafur alone was used in 18 trial comparisons (A01 IPCR, Chiba; A02 JLCSSG; A03 Mineo; A04 Park1; A05 Park2; A06 ALPI1; A07 IALT1; A08 BLT1; A09 JCOG 9304; A10 ANITA1; A11 JBR10; A12 IALT2; A13 BLT2; A14 CALGB 9633; A15 LCSG 801; A16 FLCSG 1; A17 LCSG 853; A18 BLT3) and platinum-based chemotherapy with tegafur or with tegafur plus uracil was used in eight (A19 SGACLC ACTLC1; A20 OLCSG1c; A21 SGACLC ACTLC2; A22 WJSG 2 (1+3); A23 WJSG3; A24 Xu; A25 ACTLC4a; A26 OLCSG2b). In all but one (A14 CALGB 9633), cisplatin was the platinum agent. Tegafur or tegafor plus uracil were used in combination with other agents in one trial comparison (A27 OLCSG1b) and alone in seven (A28 OLCSG1a; A29 WJSG2 (2+3); A30 WJSG4; A31 NJSGLCS; A32 OLCSG2a; A33 ACTLC4b; A34 JLCRG). Data on histology and stage were provided for all 34 trial comparisons, age and sex for 33, and performance status for 24 (Table 2). Patients were mostly men with a median age of 61 years (range 18 to 84). They tended to have good performance status and tumours that were predominantly stage I-II adenocarcinomas or squamous cell carcinomas. Staging methods would have changed over time but the methods used were the same in both treatment arms in the trials. We combined the small number of patients with stage IIIB and IV tumours (included for example, because of misclassification at diagnosis (Table 2), with stage IIIA patients for analysis; this group is subsequently referred to as stage III. The median follow-up was 5.5 years.

Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy

We identified 15 eligible trials. We included 12 trials; six from the 1995 meta-analysis and six additional ones (see Characteristics of included studies) . We could not include three for the following reasons: data were not available for one trial (Ayoub 1991), and adequate contact with investigators could not be made for

two trials (Kim 2003; Wolf 2001) (see Characteristics of excluded studies). Therefore, we included nine published and three unpublished trials, allowing 13 trial comparisons (B01 MSKCC 80-53; B02 GETCB 01CB82; B03 EORTC 08861; B04 MDA DM 87045; B05 INT 0115; B06 ALPI2; B07 IALT3; B08 BLT4; B09 ANITA2; B10 IALT4; B11 LCSG 791; B12 FLCSG 3; B13 OLCSG1d).

In nine trial comparisons (B02 GETCB 01CB82; B04 MDA DM 87045; B06 ALPI2; B07 IALT3; B08 BLT4; B09 ANITA2; B10 IALT4; B12 FLCSG 3; B13 OLCSG1d), chemotherapy was given before radiotherapy, and in four it was given concurrently with radiotherapy (B01 MSKCC 80-53; B03 EORTC 08861; B05 INT 0115; B11 LCSG 791) . Platinum and a vinca alkaloid or etoposide were used in 10 trial comparisons (B01 MSKCC 80-53; B02 GETCB 01CB82; B03 EORTC 08861; B04 MDA DM 87045; B05 INT 0115; B06 ALPI2; B07 IALT3; B08 BLT4; B09 ANITA2; B10 IALT4), platinum and tegafur plus uracil/tegafur in one (B13 OLCSG1d), and other platinum regimens in two trials (B11 LCSG 791; B12 FLCSG 3). Cisplatin was the sole platinum agent. Data on age, sex and histology were supplied for all trial comparisons, stage and extent of resection for 12, and performance status for 11. Based on these data, patients were mostly men, with good performance status, a median age of 59 years (range 27 to 81), and stage III, squamous carcinomas. We combined the few patients with stage IV tumours with stage III patients for analyses, and referred to this group as stage III. The median follow-up was 6.4 years.

Risk of bias in included studies

We only included trials with adequate methods of randomisation. We excluded trials using quasi-random methods, such as birth date. We thoroughly checked all raw data received on individual patients to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow-up. We resolved any queries and verified the final database entries by discussion with the responsible trial investigator or statistician. No RCTs were blinded due to the nature of the intervention, but the primary outcome is not likely to be influenced by the lack of blinding. We received IPD for all outcomes of interest, therefore we considered reporting bias to be low for all RCTs. We considered all included trials to be at a low risk of bias (see Figure 2 and Figure 3).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

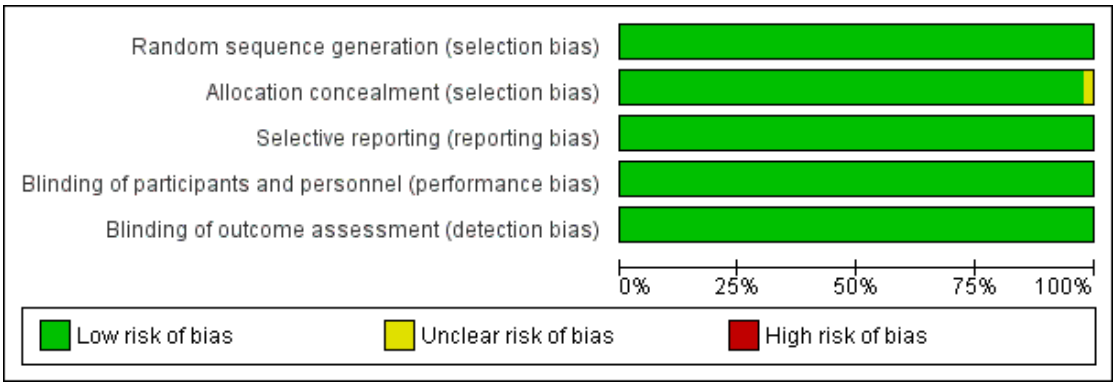
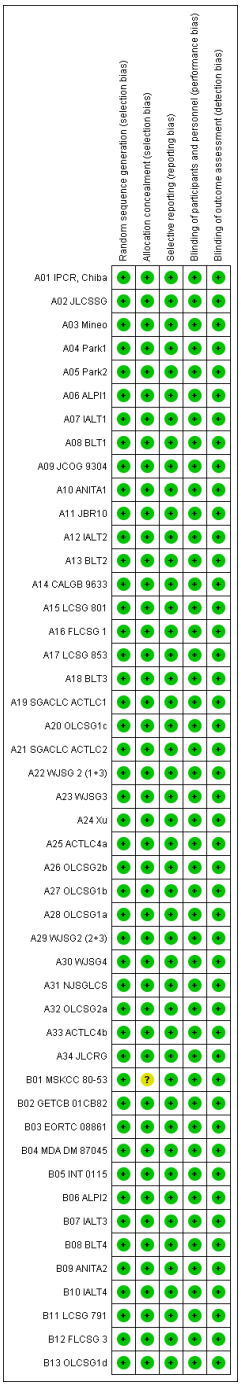


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

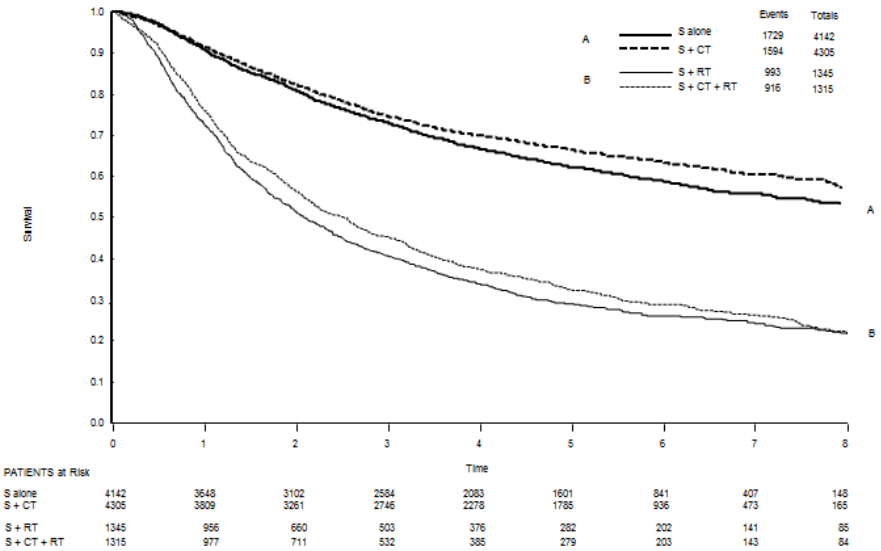


Effects of interventions

Surgery versus surgery plus adjuvant chemotherapy

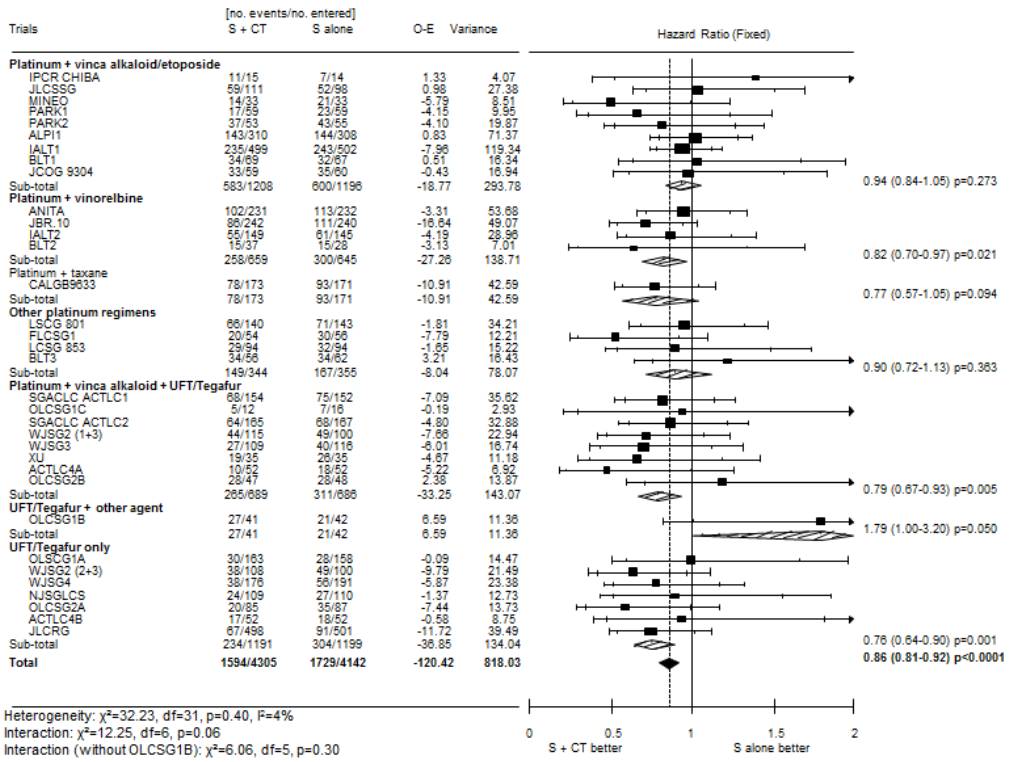
Overall survival results for the first meta-analysis were based on 34 trial comparisons and 8447 patients (3323 deaths), representing 92% of patients who were randomly assigned. The results (Analysis 1.1) show a benefit of adjuvant chemotherapy (hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.81 to 0.92, p< 0.0001; Figure 1), with minimum heterogeneity (p=0.40, I^2 = 4%). This finding represents an absolute improvement of 4% (95% CI 3 to 6) at five years, increasing overall survival from 60% to 64% (Figure 4). We noted a difference in effect by chemotherapy category (interaction p= 0.06, Figure 1), largely driven by the result of the trial comparison,A27 OLCSG1b, that alone constituted the chemotherapy category for tegafur plus uracil or tegafur plus another agent. A sensitivity analysis excluding this trial did not suggest that this drug regimen affects the effect of adjuvant chemotherapy (data not shown; interaction p= 0.30).

Figure 4. Simple (non-stratified Kaplan-Meier curves for trials of Surgery (S) and chemotherapy (CT) versus surgery alone and for trials of surgery and chemotherapy and radiotherapy (RT) versus surgery and radiotherapy.



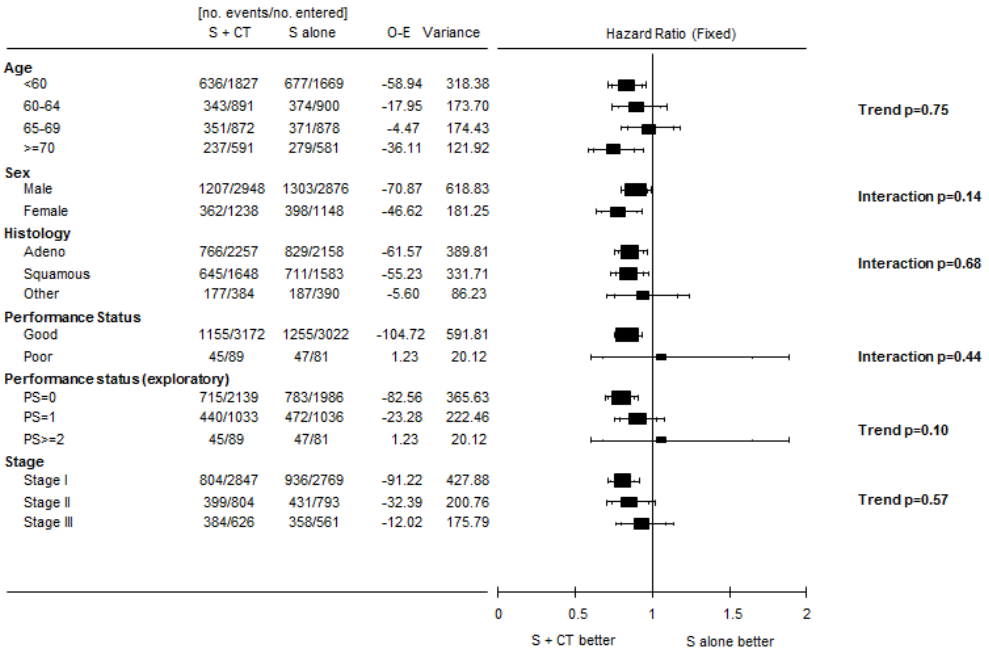
In view of the differences in the types of chemotherapy used over time and by geographical region, we grouped trial comparisons by these characteristics for exploratory analyses. We noted no clear evidence of a difference in the effect between trial comparisons included in the 1995 meta-analysis, and those included since this time (interaction p= 0.76), by accrual decade (interaction p= 0.61), or by geographical region (North America, Europe, Asia; interaction p= 0.25; data not shown). Trial comparisons using tegafur plus uracil or tegafur alone all originated in Asia, and recruited more women (n = 1293 of 3465 (37%)), and more patients with stage I tumours (3003/3673 (82%)) of adenocarcinoma histology (2505/3673 (68%)) than those that did not use tegafur plus uracil or tegafur alone (1093/4745 (23%)), (2613/4724 (55%)), (1910/4744 (40%)), respectively. However, we recorded no clear evidence of a difference in treatment effect between trial comparisons that did (3848 (45%); HR 0.80, 95% CI 0.71 to 0.90) and those that did not (4751 (55%); HR 0.89, 95% CI 0.82 to 0.97) use tegafur plus uracil or tegafur alone (overall HR 0.86, 95% CI 0.81 to 0.92, interaction p = 0.16; Figure 5), even when we excluded the trial comparison A27 OLCSG1b (data not shown; interaction p = 0.07).

Figure 5. Exploratory analyses of the effect of surgery (S) and chemotherapy (CT) versus surgery on survival, by the use of tegafur plus uracil/tegafur.



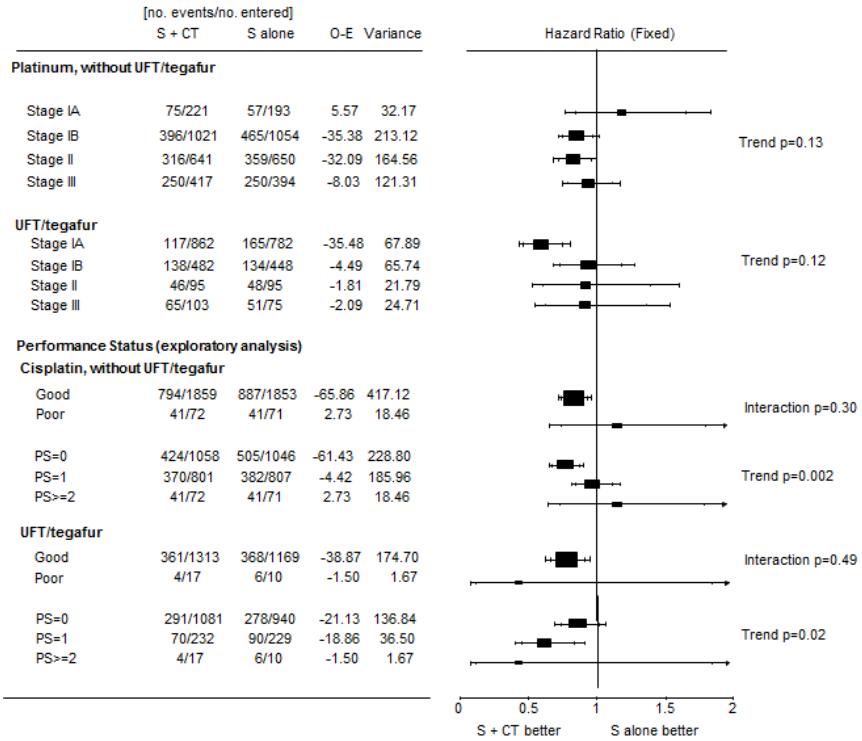
We recorded no significant evidence ($p \geq 0.10$) that any patient subgroup defined by age, sex, histology, performance status, or stage benefited more or less from adjuvant chemotherapy (Figure 6). However, because of the geographical differences in the types of patients and chemotherapy used, we undertook exploratory subgroup analyses separately for trial comparisons using platinum, without tegafur plus uracil or tegafur alone, and those using these drugs. We split stage I disease into IA and IB for all but five trial comparisons (A04 Park1; A19 SGACLC ACTLC1; A21 SGACLC ACTLC2; A26 OLCSG2b; A32 OLCSG2a) which we had to exclude since this information was not available.

Figure 6. The effect of surgery (S) and chemotherapy (CT) versus surgery on survival by patient subgroup.



For the platinum without tegafur plus uracil or tegafur alone group, although there was no evidence of difference in the effect of adjuvant chemotherapy between patients with good and poor performance status (interaction p = 0.30; Figure 7), we noted an increasing relative effect of adjuvant chemotherapy with improving performance status (trend p = 0.002; Figure 7), which was consistent across trials (data not shown; p = 0.32). However, a few patients had a poor performance status (Figure 7). The relative effect of adjuvant chemotherapy did not differ significantly by other patient subgroups, including stage (trend p = 0.13; Figure 7). Therefore, application of the overall hazard ratio to survival in the control group by stage suggests absolute improvements in 5-year survival of 3% (95% CI 2 to 5) for stage IA (from 70% to 73%), 5% (2 to 7) for stage IB (from 55% to 60%), 5% (3 to 8) for stage II (from 40% to 45%), and 5% (3 to 8) for stage III disease (from 30% to 35%). The suggested survival benefit of 3% for stage IA and the hazard ratio of 1.19 (95% CI 0.84 to 1.68) for that subgroup seemed to be contradictory. However, data are scarce for this group of patients, the CIs are very wide, and the result is not significant (p = 0.33).

Figure 7. Exploratory analyses of the effect of surgery (S) and chemotherapy (CT) versus surgery on survival, by use of tegafur plus uracil or tegafur and by stage and performance status.



In the tegafur and uracil or tegafur alone group, we noted no clear difference in the effect of adjuvant chemotherapy between patients with good or poor performance status (interaction p = 0.49; Figure 7), but did record a suggestion of an increasing relative effect of adjuvant chemotherapy with worsening performance status (trend p = 0.02; Figure 7). This trend varies substantially across trials (data not shown; p = 0.01), and few patients had a poor performance status. We noted no significant difference in the relative effect of adjuvant chemotherapy by age, sex, histology, or stage, and application of the overall HR gave absolute improvements in 5-year survival of 2% (95% CI 1 to 3) for stage IA (from 80% to 82%), 3% (1 to 4) for stage IB (from 75% to 78%), 5% (2 to 7) for stage II (from 45% to 50%), and 5% (3 to 8) for stage III disease (from 25% to 30%).

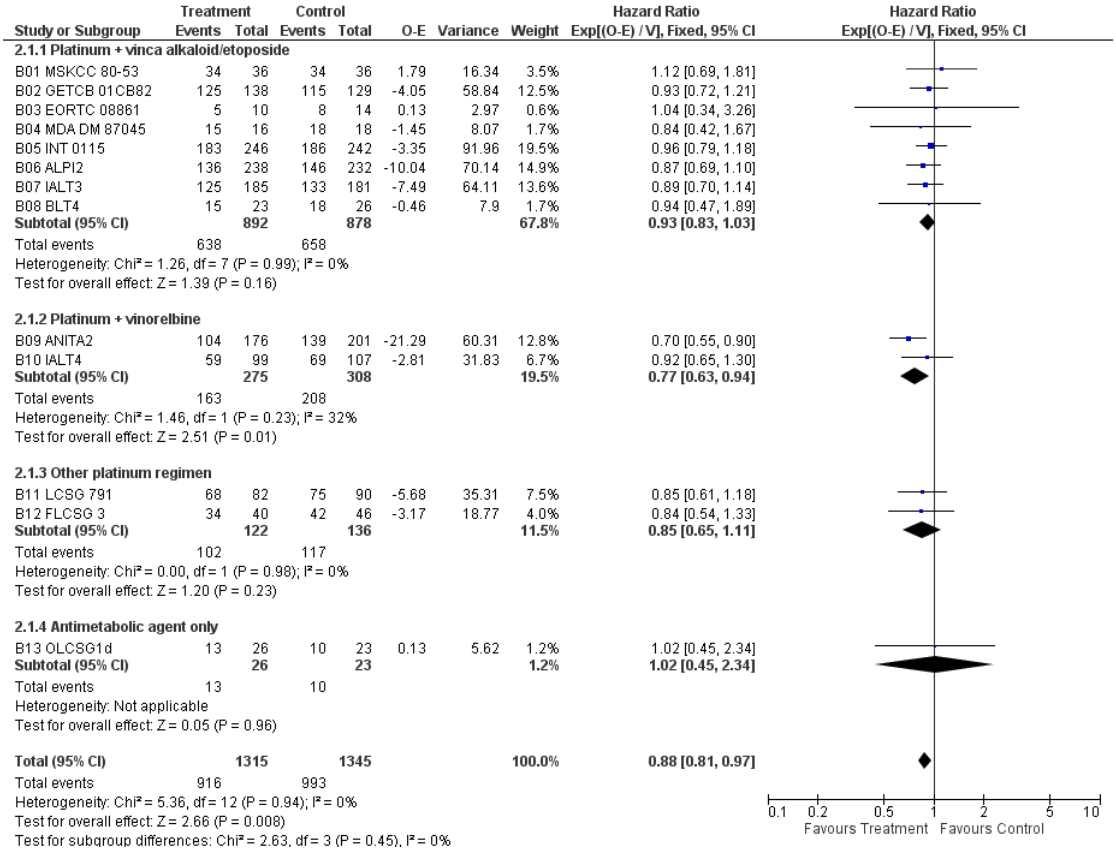
Data for recurrence-free survival were available for 18 trial comparisons (2519 events; 5379 patients) and data for locoregional (936 events; 5226 patients) and distant recurrence (1267 events; 5224 patients) for 16 trial comparisons, mostly from newer trials of platinum-based chemotherapy without tegafur plus uracil or tegafur alone. Results for recurrence-free survival (HR 0.83, 95% CI 0.77 to 0.90, p < 0.0001), time to locoregional recurrence (HR 0.75, 95% CI 0.66 to 0.85, p < 0.0001), and time to distant recurrence (HR 0.80, 95% CI 0.72 to 0.89, p = 0.0007) all significantly favoured adjuvant chemotherapy. Exclusion of the four trial comparisons that included tegafur plus uracil or tegafur alone (A23 WJSG3; A24 Xu; A33 ACTLC4b; A34 JLCRG) showed similar results (data not shown).

Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy

Overall survival analyses were based on 12 trial comparisons and 2660 patients (1909 deaths), representing 86% of patients who were randomly assigned. The results (Analysis 2.1) showed a clear benefit of adjuvant chemotherapy (HR 0.88, 95% CI 0.81 to 0.97, p = 0.009; Figure 8), with little heterogeneity (p = 0.95, I^2 = 0%). This finding represents an absolute benefit of 4% (95% CI 1 to 8) at 5 years, increasing survival from 29% to 33% (Figure 4). We recorded no evidence of a differential effect by chemotherapy category (interaction p = 0.45; Figure 8) or the extent of resection achieved: trials with complete resection only (6 trials, 2005 patients; HR 0.87, 95% CI 0.78 to 0.97) versus trials with complete or incomplete resection (6 trials, 655 patients; HR 0.92, 95% CI 0.78 to 1.08); interaction p = 0.63. Furthermore, an exploratory analysis suggests that the timing of chemotherapy in relation to

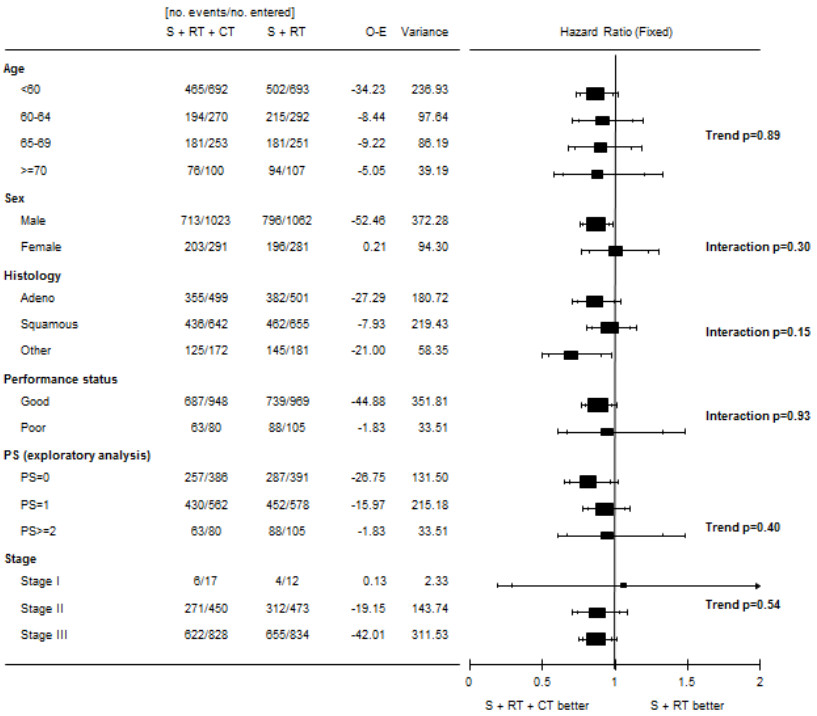
radiotherapy is unimportant: trials with chemotherapy before radiotherapy (9 trials, 1928 patients; HR 0.86, 95% CI 0.77 to 0.96) versus trials with concomitant chemoradiotherapy (3 trials, 732 patients; HR 0.95, 95% CI 0.81 to 1.12); interaction p = 0.30.

Figure 8. Forest plot of comparison: 2 surgery + radiotherapy versus surgery + radiotherapy + chemotherapy, outcome: 2.1 Survival.



The relative effect of adjuvant chemotherapy did not differ significantly by age, sex, histology, performance status, or stage (Figure 9). Data for recurrence-free survival, and locoregional and distant recurrence were available for eight trial comparisons (2247 patients). Results for recurrence-free survival (1673 events, 2247 patients; HR 0.85, 95% CI 0.77 to 0.93, p = 0.0006), time to locoregional recurrence (533 events; HR 0.79, 95% CI 0.67 to 0.94, p = 0.008), and time to distant recurrence (806 events; HR 0.75, 95% CI 0.66 to 0.87, p < 0.0001) all showed a significant benefit of adjuvant chemotherapy.

Figure 9. The effect of surgery (S) and radiotherapy (RT) and chemotherapy (CT) versus surgery and radiotherapy on survival by patient subgroup.



DISCUSSION

Summary of main results

Our results show a benefit of adjuvant chemotherapy after surgery, which has been already shown in some large trials but not in others (for example, A06 ALPI1 and A14 CALGB 9633). They also show a benefit of chemotherapy in the presence of postoperative radiotherapy. The absolute survival improvements of 4% at five years are fairly modest, but might result in 10,000 to 16,000 more patients alive at five years (Datta 2003). The results of the two meta-analyses are based on data from 47 comparisons in 33 trials and 11,107 patients with non-small cell lung cancer (NSCLC), which is more than three times that available in the NSCLC Collaborative Group 1995. In these meta-analyses, we have an opportunity to bring together most trials undertaken during the past few decades, and to assess the effectiveness of adjuvant chemotherapy in patients with NSCLC worldwide.

Although we noted no significant difference in effect between chemotherapy categories in the first meta-analysis, results for the trials that used older vinca alkaloids (vinblastine, vindesine, vincristine), etoposide, or other platinum combinations were somewhat uncertain, whereas trials using a combination of platinum and vinorelbine provided slightly more reliable evidence of benefit to inform present clinical practice (Figure 1; Figure 8). The results for chemotherapy with tegafur plus uracil or tegafur alone are similar to those for platinum-based regimens. However, results come largely from older studies in Asian populations, which are increasingly showing differences in their response to treatment (Sekine 2008), and so cannot be extrapolated to modern practice in non-Asian patients. A trial of tegafur plus uracil or tegafur alone in patients with stage IA, adenocarcinoma from non-Asian countries would be beneficial in this context. Results of an ongoing trial might establish the relative merits of carboplatin-paclitaxel and tegafur plus uracil in Asian patients (Toyooka 2009).

Guidelines from Cancer Care Ontario and American Society of Clinical Oncology (ASCO) (Pisters 2007) recommend that adjuvant cisplatin-based chemotherapy is given to patients with stage II and IIIA NSCLC.

These guidelines state that evidence is insufficient to make recommendations for patients with stage IA disease, and one meta-analysis (Pignon 2008) reported a significant decrease in the effect of adjuvant cisplatin-based chemotherapy by stage, largely driven by the stage IA result. This meta-analysis does not show signifi-

cant differences in the effect of platinum chemotherapy (without tegafur plus uracil or tegafur alone) by stage or significantly poorer survival in patients with stage IA disease (Figure 7). The evidence in stage IA tumours remains scarce until results from further trials are available.

The ASCO guidelines also state that none of the studies reviewed showed a significant benefit of adjuvant chemotherapy in patients with stage IB tumours. By contrast, our estimate of the effect of platinum-based adjuvant chemotherapy in patients with stage IB tumours is based on a substantial number of events and is similar to estimates for patients with stage II and III tumours (Figure 7). Since we did not collect data for tumour size, patients with larger stage IB tumours, who would be classed as stage II in the 7th edition of the TNM staging system (IASLC 2009) and might achieve a greater benefit from adjuvant chemotherapy are potentially included. In the absence of comorbidities and contraindications to chemotherapy, our findings show that adjuvant platinum-based chemotherapy may be considered as a treatment option for patients at high risk of recurrence, ie, those with stage IB, II, or III disease. Whethercisplatin-based chemotherapy should be used in patients with stage IA disease remains uncertain, since the scarcity of data did not allow us to distinguish reliably between a benefit, a detriment, or no effect. Most patients had good performance status and the benefit was clear in this group. A small increasing effect of platinum-based chemotherapy with better performance status was also apparent in this and another meta-analysis (Pignon 2008), but was not confirmed in trials using tegafur plus uracil or tegafur alone, or those that included postoperative radiotherapy. Nevertheless, these results could suggest cautious use of platinum-based chemotherapy in less fit patients. Despite the amount of data collected, some of the subgroup analyses lacked power.

The benefits of adjuvant chemotherapy have been reported to be attenuated in long-term results (Arriagada 2010; Butts 2010), however, we do not have much data beyond five years. The potential benefit of adjuvant chemotherapy should always be balanced with possible toxic effects for the individual patient. We were unable to assess toxic effects of treatment in this study. Moreover, extrapolation of the results to patients with comorbidities is uncertain because most of the patients included in these meta-analyses had mild or no comorbidities. Quality of life was measured in only a few trials and so could not be reviewed.

Overall completeness and applicability of evidence

Surgery versus surgery plus adjuvant chemotherapy

We identified 35 eligible trials and included 26. We could not include nine trials; five could not be included as data were not available; two could not be included as adequate contact could not be made with the trial investigators; and two were published too recently to be included (but will be included in a subsequent update). Therefore this represents 92% of all patients who were randomised into eligible trials.

Surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy

We identified 15 eligible trials and included 12. We could not include three trials; one could not be included as data were not available; and two could not be included as adequate contact could not be made with the trial investigators. Therefore this represents 86% of all patients who were randomised into eligible trials.

Quality of the evidence

The trials included in this update show an overall low risk of bias in the domains we considered to be most important; those being adequate sequence generation and allocation concealment. Blinding was not appropriate due to the nature of the treatments and any issues surrounding the reporting of incomplete outcome data, selective outcome reporting or attrition bias were overcome by the collection of individual participant data. We are confident that further research is unlikely to change the findings. The studies were well designed and conducted, address the review question and the effects are consistent across trials. The impact of any data we have not been able to include in our analyses is small.

Potential biases in the review process

We aimed to include all trials, unpublished and unpublished, regardless of the language they were published in. We collected IPD for all included trials. The first meta-analysis (surgery versus surgery plus adjuvant chemotherapy) included 92% of eligible data and the second meta-analysis (surgery plus radiotherapy versus surgery plus radiotherapy plus adjuvant chemotherapy) included 86% of eligible data. Had we been able to include this extra data, it is unlikely they would have had an impact on these results. We checked and verified data against the published results. We resolved any queries and verified the final database by each trial investigator or statistician. We deemed all included trials to have a low risk of bias using the 'Risk of bias' tool.

Agreements and disagreements with other studies or reviews

This is an update and extension of a previous systematic review and meta-analysis. The results are still in favour of the addition of chemotherapy to surgery and postoperative radiotherapy, however these results are more up to date and contain more than three times more patients than that available in 1995.

AUTHORS' CONCLUSIONS

Implications for practice

The addition of chemotherapy following surgery and postoperative radiotherapy gave a 4% improvement in 5-year survival from 29% to 33%. This benefit should be balanced against possible toxicity and quality of life. Where toxicity was assessed and mentioned in the publications, it was thought to be manageable. This 4% increase does not seem to vary with the timing of chemotherapy in relation to radiotherapy, extent of surgery, or by patient subgroup (Figure 6; Figure 9). The lower survival rates than those in the surgery and chemotherapy meta-analysis are most likely because patients with stage III tumours predominate and the incomplete resection rate is higher (Table 2). A previous meta-analysis (PORT 1998; PORT 2005) has shown that postoperative radiotherapy has a detrimental effect on survival, particularly for early stage tumours, but old radiotherapy techniques were used.

Implications for research

This meta-analysis was not designed to study the effect of postoperative radiotherapy, but has shown that the effect of chemotherapy is similar, irrespective of what locoregional treatment is used: surgery alone or surgery plus postoperative radiotherapy. Randomised trials are needed to assess whether modern radiotherapy is effective as an adjuvant treatment. Since this review was completed, we have found further eligible trials (NATCH 2010; Wang 2009; Zheng 2011); (see Characteristics of studies awaiting classification and Characteristics of excluded studies) it is hoped that we will be able to include these trials in a future update of this project.

ACKNOWLEDGEMENTS

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Imaizumi M. Postoperative adjuvant cisplatin, vindesine, plus uracil-tegafur chemotherapy increased survival of patients with completely resected p-stage I non-small cell lung cancer. *Lung Cancer* 2005;**49**:85–94.

A26 OLCSG2b *{published and unpublished data}*
Nakagawa K, Tada H, Akash iA, Yasumitsu T, Iuchi K, Taki T, et al. Randomised study of adjuvant chemotherapy for completely resected p stage I-IIIa non-small cell lung cancer. *British Journal of Cancer* 2006;**95**:817–21.

A27 OLCSG1b *{published and unpublished data}*
Sawamura K, Mori T, Doi O, Yasumitsu T, Kuwahara O, Kuwabara M, et al. A prospective randomized controlled study of the postoperative adjuvant therapy for non-small cell lung cancer. *Lung Cancer* 1988;**4**:A166.

A28 OLCSG1a *{published and unpublished data}*
Sawamura K, Mori T, Doi O, Yasumitsu T, Kuwahara O, Kuwabara M, et al. A prospective randomized controlled study of the postoperative adjuvant therapy for non-small cell lung cancer. *Lung Cancer* 1988;**4**:A166.

A29 WJSG2 (2+3) *{published and unpublished data}*
Wada H, Hitomi S, Takashi T, : West Japan Study Group for Lung Cancer Surgery. Adjuvant chemotherapy after complete resection in non-small cell lung cancer. *Journal of Clinical Oncology* 1996;**14**:1048–54.

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Nakagawa M, Tanaka F, Tsubota N, Ohta M, Takao M, Wada H. A randomised phase III trial of adjuvant chemotherapy with UFT for completely resected pathological stage I non-small cell lung cancer: the West Japan Study Group for Lung Cancer Surgery (WJSG) - the 4th study. *Annals of Oncology* 2005;**16**:75–80.

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Endo C, Saitoi Y, Iwanawi H, Tsushima T, Imai T, Kawamura M, et al. A randomized trial of postoperative UFT in p stage I, II non-small cell lung cancer: North-East Japan Study Group for Lung Cancer Surgery. *Lung Cancer* 2003;**40**:181–6.

A32 OLCSG2a *{published and unpublished data}*
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A33 ACTLC4b *{published and unpublished data}*
Imaizumi M. Postoperative adjuvant cisplatin, vindesine, plus uracil-tegafur chemotherapy increased survival of patients with completely resected p-stage I non-small cell lung cancer. *Lung Cancer* 2005;**49**:85–94.

A34 JLCRG *{published and unpublished data}*
Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, et al. A randomised trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *New England Journal of Medicine* 2004;**350**(17):1713–21.

B01 MSKCC 80-53 *{published and unpublished data}*
Pisters KMW, Kris MG, Gralla RT, Hilaris B, McCormack PM, Bains MS. Randomized trial comparing post-operative chemotherapy with vindesine and cisplatin plus thoracic irradiation with irradiation alone in stage III (N2) non-small cell lung cancer. *Journal of Surgical Oncology* 1994;**56**: 236–241.

B02 GETCB 01CB82 *{published and unpublished data}*
Dautzenberg B, Chastang C, Arriagada R, Le Chevalier T, Belpomme D, Hurdebourcq M, et al. Adjuvant radiotherapy versus combined sequential chemotherapy followed by radiotherapy in the treatment of resected non-small cell lung cancer. *Cancer* 1995;**76**:779–86.

B03 EORTC 08861 *{unpublished data only}*
EORTC Lung Cancer Cooperative Group. Phase III randomized trial of adjuvant radiotherapy vs radiotherapy plus chemotherapy with DDP/VDS vs no adjuvant therapy in patients with completely resected non-small cell lung cancer.

B04 MDA DM 87045 *{unpublished data only}*
MD Anderson Cancer Centre. Phase III randomized comparison of chest irradiation vs combination chemotherapy with cyclophosphamide/etoposide/cisplatine (CEP) followed by chest irradiation in patients with partially resected stage II/III limited non small cell lung cancer.

B05 INT 0115 *{published and unpublished data}*
Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brookes BJ, et al. Postoperative adjuvant therapy in patients with stage II or IIIa non-small cell lung cancer. *New England Journal of Medicine* 2000;**343**:1217–22.

B06 ALPI2 *{published and unpublished data}*
Scagliotti GV, Fossati R, Torri V, Crinò L, Giaccone G, Silvano G, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIa non-small cell lung cancer. *Journal of the National Cancer Institute* 2003;**95**(19):1453–61.

B07 IALT3 *{published and unpublished data}*
Arriagada R, Dunant A, Pignon J-P, Bergman B, Chabowski M, Grunenwald D, et al. Long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. *Journal of Clinical Oncology* 2010;**28**:35–42.
The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *New England Journal of Medicine* 2004;**350**:351–60.

B08 BLT4 *{published and unpublished data}*
Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MKB, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *European Journal of Cardio-Thoracic Surgery* 2004;**26**: 173–82.

B09 ANITA2 *{published and unpublished data}*
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B10 IALT4 *{published and unpublished data}*
Arriagada R, Dunant A, Pignon J-P, Bergman B, Chabowski M, Grunenwald D, et al. Long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. *Journal of Clinical Oncology* 2010;**28**:35–42.
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B11 LCSG 791 *{published and unpublished data}*
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B12 FLCSG 3 *{unpublished data only}*
Niiranen, Kouri M, Pyrhonen S, Mattson K. Postsurgical radiotherapy versus postsurgical radiotherapy plus chemotherapy for non-small cell lung cancer.

B13 OLCSG1d *{published and unpublished data}*
Sawamura K, Mori T, Doi O, Yasumitsu T, Kawahara O, Kuwabara M, et al. A prospective randomized controlled study of the postoperative adjuvant therapy for non-small cell lung cancer. *Lung Cancer* 1988;**4**:A166.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

A01 IPCR, Chiba

Methods	RCT: 1985 to 1991
Participants	29 patients Stage NK
Interventions	surgery vs surgery + chemotherapy cisplatin 80 mg/m^2 vindesine 3 mg/m^2 mitomycin c 8 mg/m^2 Complete and incomplete resection
Outcomes	Overall survival
Notes	> 2 cycles of chemotherapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelope
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A02 JLCSSG

Methods	RCT: 1986 to 1988
Participants	209 patients Stage III

A02 JLCSSG (*Continued*)

Interventions	surgery vs surgery + chemotherapy 2-3 cycles of chemotherapy cisplatin 80 mg/m^2 vindesine 6 mg/m^2
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Permuted block randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A03 Mineo

Methods	RCT: 1988 to 1994
Participants	66 patients Stage IB
Interventions	surgery vs surgery + chemotherapy 6 cycles of chemotherapy cisplatin 100 mg/m^2etoposide 120 mg/m^2 Complete resection
Outcomes	Overall survival 5 year recurrence-free survival Recurrence rates Cause of death
Notes	140 patients in trial, only 66 reported at time of data collection, therefore only 66 patients included

A03 Mineo (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central computer randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A04 Park1

Methods	RCT: 1989 to 1998
Participants	118 patients Stage I
Interventions	surgery vs surgery + chemotherapy 3-4 cycles of chemotherapy mitomycin c 10mg/m^2 vinblastin 6 mg/m^2 cisplatin 100 mg/m^2 Complete resection
Outcomes	Overall survival Recurrence-free survival Death from any cause Toxicity
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation

A04 Park1 (*Continued*)

Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A05 Park2

Methods	RCT: 1989 to 1998
Participants	108 patients Stage IIIA
Interventions	surgery vs surgery + chemotherapy 3-4 cycles of chemotherapy cisplatin 100 mg/m^2 mitomycin c 10 mg/m^2 vinblastine 6 mg/m^2 Complete resection
Outcomes	Overall survival Recurrence-free survival
Notes	2 arms of a 3-arm trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A06 ALPI1

Methods	RCT: 1994 to 1999
Participants	618 patients Stage I-IIIA
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy cisplatin 100 mg/m^2 vindesine 6 mg/m^2 mitomycin 8 mg/m^2 Complete resection
Outcomes	Overall survival Recurrence-free survival Toxicity
Notes	1088 patients analysed, 470 received RT, only 618 patients relevant to this trial comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A07 IALT1

Methods	RCT: 1995 to 2001
Participants	1001 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 3 or 4 cycles of chemotherapy cisplatin 80, 100 or 120 mg/m^2 and vindesine 3 mg/m^2

A07 IALT1 (*Continued*)

	or vinblastine 8 mg/m^2 or etoposide 300 mg/m^2 Complete resection
Outcomes	Overall survival Recurrence-free survival Causes of death
Notes	1867 patients randomised to trial, 1001 patients in this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A08 BLT1

Methods	RCT: 1995 to 2001
Participants	136 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy cisplatin 50 mg/m^2 mitomycin 6 mg/m^2 vinblastine 6 mg/m^2 or cisplatin 80 vindestine 6 Complete resection
Outcomes	Overall survival

A08 BLT1 (*Continued*)

Notes	381 patients randomised in surgical setting, 136 relevant to this trial comparison	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A09 JCOG 9304

Methods	RCT: 1994 to 1999	
Participants	119 patients Stage I-III	
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy cisplatin 80 mg/m^2 vindesine 3 mg/m^2 Complete and incomplete resection	
Outcomes	Overall survival	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Randomisation by blocks within each institution

A09 JCOG 9304 (*Continued*)

Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A10 ANITA1

Methods	RCT: 1994 to 2000
Participants	463 patients Stage IB-IIIA
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy cisplatin 100 mg/m^2 vinorelbine 180 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	840 patients randomised in trial, 436 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central computer randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A11 JBR10

Methods	RCT: 1994 to 2001
Participants	482 patients Stage IB-II
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy cisplatin 50 mg/m^2 vinorelbine 25mg/m^2 (initial patients received 30 mg/m^2) Complete resection
Outcomes	Overall survival Recurrence-free survival
Notes	Updated survival published in 2010, data included here is as published in 2005

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A12 IALT2

Methods	RCT 1995 to 2001
Participants	294 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 3 or 4 cycles of chemotherapy cisplatin 80, 100 or 120 mg/m^2 vinorelbine 30 mg/m^2 Complete resection

A12 IALT2 (*Continued*)

Outcomes	Overall survival Recurrence-free survival Causes of death
Notes	1867 patients randomised to trial, 294 patients in this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A13 BLT2

Methods	RCT 1995 to 2001
Participants	65 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy cisplatin 80 mg/m^2 vinorelbine 60 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	381 patients randomised in surgical setting, 65 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation

A13 BLT2 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A14 CALGB 9633

Methods	RCT: 1996 to 2003
Participants	344 patients Stage IB
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy carboplatin 6mg/mL over 45-60 min vinorelbine 30 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A15 LCSG 801

Methods	RCT: 1980 to 1986
Participants	283 patients Stage I
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy cisplatin 60 mg/m^2 doxorubincin 40 mg/m^2 cyclophosphamide 400 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	4 cycles of chemotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	N/A IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A16 FLCSG 1

Methods	RCT: 1982 to 1987
Participants	110 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 6 cycles of chemotherapy cisplatin 40 mg/m^2 doxorubicin 40 mg/m^2 cyclophosphamide 400 mg/m^2
Outcomes	Overall survival

A16 FLCSG 1 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A17 LCSG 853

Methods	RCT: 1985 to 89
Participants	188 patients Stage II-III
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy cisplatin 60 mg/m^2 doxorubicin 40 mg/m^2 cyclophosphamide 400 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation

A17 LCSG 853 (*Continued*)

Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A18 BLT3

Methods	RCT: 1995 to 2001
Participants	118 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy cisplatin 50 mg/m^2 mitomycin 6 mg/m^2 ifosphamide 3 mg/m^2 Complete resection
Outcomes	Overall survival
Notes	381 patients randomised in surgical setting, 118 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A19 SGACLC ACTLC1

Methods	RCT: 1982 to 1985
Participants	306 patients Stage NK
Interventions	surgery vs surgery + chemotherapy 10 cycles of chemotherapy cisplatin 0.08 mg/kg mitomycin 2 mg/kg tegafur 12 mg/kg daily treatment > 6 months
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A20 OLCSG1c

Methods	RCT: 1982 to 1987
Participants	28 patients Stage II
Interventions	surgery vs surgery + chemotherapy 1 cycles of chemotherapy cisplatin 80 mg/m^2 tegafur 600-800 mg/m^2, daily treatment > 1 year Complete resection
Outcomes	Overall survival

A20 OLCSG1c (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A21 SGACLC ACTLC2

Methods	RCT: 1985 to 1987
Participants	332 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy cisplatin 66 mg/m^2 doxorubicin 26 mg/m^2 UFT 8 mg/kg, daily treatment > 6 months Complete and incomplete resection
Outcomes	Overall survival
Notes	Unpublished
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelope
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes

A21 SGACLC ACTLC2 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A22 WJSG 2 (1+3)

Methods	RCT:1985 to 1988
Participants	323 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 1 cycle of chemotherapy cisplatin 50mg/m^2 vindesine 6-9mg/m^2 UFT 400mg/m^2 , daily treatment 1 year Complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A23 WJSG3

Methods	RCT: 1988 to 1989
Participants	225 patients Stage I-II
Interventions	surgery vs surgery + chemotherapy 2 cycles of chemotherapy cisplatin 80 mg/m^2 vindesine 2-3 mg/m^2 mitomycin 8 mg/m^2 tegafur and uracil 400 mg/m^2 (total), daily treatment for 1 year Complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A24 Xu

Methods	RCT: 1989 to 1992
Participants	70 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy 4 cycles of chemotherapy cisplatin 100 mg/m^2 cyclophosphamide 300 mg/m^2 vincristine 1.4 mg/m^2 doxorubicin 50 mg/m^2

A24 Xu (*Continued*)

	lomustine 50 mg/m^2 oral tegaful 600-900 mg/m^2 (total), daily treatment for 1 year Complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelope
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A25 ACTLC4a

Methods	RCT: 1982 to 1988
Participants	104 patients Stage I
Interventions	surgery vs surgery + chemotherapy cisplatin 80 mg/m^2, 1 cycle vindesine 6 mg/m^2 , 2 cycles tegafur and uracil 400 mg/m^2 (total), daily treatment for 2 years Complete resection
Outcomes	Overall survival Recurrence-free survival Toxicity
Notes	156 patients randomised in trial, 104 patients relevant to this trial comparison

Risk of bias

A25 ACTLC4a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A26 OLCSG2b

Methods	RCT: 1992 to 1994
Participants	95 patients Stage II-III
Interventions	surgery vs surgery + chemotherapy 2 cycles of chemotherapy cisplatin 80 mg/m^2 vindesine 6 mg/m^2 tegafur and uracil 400 mg/m^2 (total), daily treatment for 1 year Complete resection
Outcomes	Overall survival
Notes	267 patients randomised in trial, 95 patients relevant to this trial comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes

A26 OLCSG2b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A27 OLCSG1b

Methods	RCT: 1982 to 1986
Participants	83 patients Stage II-III
Interventions	surgery vs surgery + chemotherapy 3 cycles of chemotherapy doxorubicin 100 mg/m^2 mitomycin 20 mg/m^2 tegafur 600-800 mg/m^2, daily treatment followed by tegafur 600-800 mg/m^2 daily treatment > 1 year Complete and incomplete resection
Outcomes	Overall survival Recurrence-free interval
Notes	363 patients randomised in trial, 83 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A28 OLCSG1a

Methods	RCT: 1982 to 1987
Participants	321 patients Stage I
Interventions	surgery vs surgery + chemotherapy tegafur 600-800 mg/m^2 , daily treatment > 1 year Complete resection
Outcomes	Overall survival Recurrence-free interval
Notes	363 patients randomised in trial, 321 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A29 WJSG2 (2+3)

Methods	RCT: 1985 to 1988
Participants	208 patients Stage I-III
Interventions	surgery vs surgery + chemotherapy tegafur and uracil 400mg/m^2 , daily treatment for 1 year Complete resection
Outcomes	Overall survival
Notes	323 patients randomised in trial, 208 patients relevant to this comparison

A29 WJSG2 (2+3) (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A30 WJSG4

Methods	RCT: 1991 to 1994
Participants	367 patients Stage I-II
Interventions	surgery vs surgery + chemotherapy tegafur and uracil 400 mg/m^2 (total), daily treatment for 1 year Complete resection
Outcomes	Overall survival
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

A30 WJSG4 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A31 NJSGLCS

Methods	RCT: 1992 to 1994
Participants	219 patients Stage I-II
Interventions	surgery vs surgery + chemotherapy tegafur and uracil 260 mg/m^2 total or 400 mg/m^2 total, daily treatment for 2 years Complete resection
Outcomes	Overall survival Recurrence-free survival Toxicity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A32 OLCSG2a

Methods	RCT: 1992 to 1994
Participants	172 patients Stage I

A32 OLCSG2a (*Continued*)

Interventions	surgery vs surgery + chemotherapy tegafur and uracil 400 mg/m^2 (total), daily treatment for 1 year Complete resection
Outcomes	Overall survival Recurrence-free survival
Notes	267 patients randomised in trial, 172 relevant to this comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A33 ACTLC4b

Methods	RCT: 1992 to 1995
Participants	104 patients Stage I
Interventions	surgery vs surgery + chemotherapy tegafur and uracil 400 mg/m^2 (total), daily treatment for 2 years Complete resection
Outcomes	Overall survival Recurrence-free survival Safety
Notes	156 patients randomised in trial, 104 relevant to this comparison

Risk of bias

A33 ACTLC4b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

A34 JLCRG

Methods	RCT: 1994 to 1997
Participants	999 patients Stage I
Interventions	surgery vs surgery + chemotherapy tegafur and uracil 250 mg/m^2 (total), daily treatment for 2 years Complete and incomplete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

B01 MSKCC 80-53

Methods	RCT: 1981 to 1987
Participants	72 patients Stage III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 120mg/m^2 vindesine 9 mg/m^2 4 cycles of chemotherapy radiotherapy 46 Gy complete and incomplete resections
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Not reported (unpublished)
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B02 GETCB 01CB82

Methods	RCT: 1982 to 1986
Participants	267 patients Stage I-III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy doxorubicin 40 mg/m^2 vincristine 1.2 mg/m^2 cisplatin 75 mg/m^2 lomustine 80 mg/m^2(total) alternating with cyclophosphamide 600 mg/m^2 3 cycles of chemotherapy given before radiotherapy radiotherapy 60-65 Gy in 30-33 fractions complete and incomplete resection
Outcomes	Overall survival Recurrence-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for all outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B03 EORTC 08861

Methods	RCT: 1986 to 1990
Participants	22 patients Stage IIB-IIIA
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 100 mg/m^2 vindesine 6 mg/m^2 4 cycles of chemotherapy, 2 given before radiotherapy

B03 EORTC 08861 (*Continued*)

	radiotherapy 56 Gy in 28 fractions complete resection
Outcomes	Overall survival
Notes	unpublished

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for all outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B04 MDA DM 87045

Methods	RCT: 1987 to 1993
Participants	34 patients Stage NK
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 50-100 mg/m^2 etoposide 60-120 mg/m^2 cyclophosphamide 300-600 mg/m^2 CT given before RT, number of cycles unknown radiotherapy 50-60 Gy in 25-33 fractions incomplete resection
Outcomes	Overall survival Recurrence-free survival
Notes	Unpublished

Risk of bias

B04 MDA DM 87045 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B05 INT 0115

Methods	RCT: 1991 to 1997
Participants	488 patients Stage II-IIIA
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 60 mg/m^2 etoposide 360 mg/m^2 4 cycles of chemotherapy given concomitantly with radiotherapy radiotherapy 56 Gy in 28 fractions complete resection
Outcomes	Overall survival Recurrence-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes

B05 INT 0115 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B06 ALPI2

Methods	RCT 1994-99
Participants	470 patients Stage I-IIIA
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 100 mg/m^2 vindesine 6 mg/m^2 mitomycin c 8 mg/m^2 3 cycles of chemotherapy given before radiotherapy radiotherapy 50-54 Gy in 25-27 fractions complete resection
Outcomes	Overall survival Recurrence-free survival Toxicity
Notes	1088 patients analysed, 470 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

B07 IALT3

Methods	RCT: 1995 to 2001
Participants	1001 patients Stage I-III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin (80, 100 or 120 mg/m^2) and vindesine 3 mg/m^2 or vinblastine 8 mg/m^2 or etoposide 300 mg/m^2 3 or 4 cycles of chemotherapy given before radiotherapy radiotherapy < 60 Gy complete resection
Outcomes	Overall survival Recurrence-free survival Causes of death
Notes	1867 patients randomised to trial, 366 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B08 BLT4

Methods	RCT: 1995 to 2001
Participants	49 patients Stage I-III

B08 BLT4 (*Continued*)

Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin (80, 100 or 120mg/m^2) and vindesine mitomycin c 8 mg/m^2 3 cycles of chemotherapy given before radiotherapy radiotherapy < 60 Gy complete resection
Outcomes	Overall survival Recurrence-free survival
Notes	381 patients randomised to trial, 49 patients relevant to this trial comparison

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B09 ANITA2

Methods	RCT: 1994 to 2000
Participants	377 patients Stage IB-IIIA
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 100 mg/m^2 vinorelbine 120 mg/m^2 4 cycles of chemotherapy given before radiotherapy radiotherapy 45-60 Gy in 23-30 fractions complete resection
Outcomes	Overall survival Recurrence-free survival

B09 ANITA2 (*Continued*)

Notes	840 patients randomised in trial, 377 patients relevant to this trial comparison	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

B10 IALT4

Methods	RCT: 1994 to 2001	
Participants	206 patients Stage I-III	
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin (80, 100 or 120mg/m^2) vinorelbine 30 mg/m^2 3 or 4 cycles of chemotherapy given before radiotherapy radiotherapy < 60 Gy complete resection	
Outcomes	Overall survival Recurrence-free survival Causes of death	
Notes	1867 patients randomised in trial, 206 patients relevant to this trial comparison	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation

B10 IALT4 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

B11 LCSG 791

Methods	RCT: 1979 to 85
Participants	172 patients Stage I-III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cyclophosphamide 400 mg/m^2 doxorubicin 40 mg/m^2 cisplatin 40 mg/m^2 6 cycles of chemotherapy, concomitant chemotherapy-radiotherapy for 1st 2 cycles of chemotherapy radiotherapy 40 Gy in 10 fractions incomplete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B11 LCSG 791 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B12 FLCSG 3

Methods	RCT: 1982 to 1987
Participants	86 patients Stage I-III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cyclophoshamide 400 mg/m^2 doxorubicin 40 mg/m^2 cisplatin 40 mg/m^2 8 cycles of chemotherapy, 2 given before radiotherapy radiotherapy 55 Gy in 20 fractions incomplete resection
Outcomes	Overall survival
Notes	unpublished

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelope
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding

B13 OLCSG1d

Methods	RCT: 1983 to 1987
Participants	49 patients Stage III
Interventions	surgery + radiotherapy vs surgery + radiotherapy + chemotherapy cisplatin 80 mg/m^2(given once) tegafur* 600-800 mg/m^2 (daily treatment) chemotherapy before radiotherapy, unknown number of cycles of chemotherapy radiotherapy 40 Gy in 20 fractions complete resection
Outcomes	Overall survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Data checks on IPD provided suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelope
Selective reporting (reporting bias)	Low risk	IPD supplied for outcomes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial not blinded due to nature of intervention, primary outcome not likely to be influenced by lack of blinding

Gy - Gray, unit of radiotherapy dose
IPD - Individual participant data
NK - not known
N/A - not available
UFT - Uracil/tegafur
RCT - randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ayoub 1991	Data not available
Clerici 1991	Data not available
EORTC 08922	Data not available
Ichinose 1991	Data not available
Kim 2003	No contact with trialist established
NCCTG 852451	Data not available
Ueda 2004	No contact with trialist established
Wang 2009	Trial discovered too late to be included in this analysis
Wolf 2001	No contact with trialist established
Wu 2009	Trial discovered too late to be included in this analysis
Zarogoulidis 1996	No contact with trialist established

Characteristics of studies awaiting assessment *[ordered by study ID]*

NATCH 2010

Methods	Randomised controlled trial
Participants	423 patients relevant
Interventions	Surgery + chemotherapy vs surgery
Outcomes	Recurrence-free survival
Notes	

Zheng 2011

Methods	Randomised controlled trial
Participants	70 patients
Interventions	Surgery + chemotherapy vs surgery

Zheng 2011 (*Continued*)

Outcomes	Overall survival
Notes	

Characteristics of ongoing studies *[ordered by study ID]*

CALGB 30506

Trial name or title	CALGB 30506: Phase III randomised study of adjuvant chemotherapy versus observation in patients with early stage non-small cell lung cancer
Methods	Randomised controlled trial
Participants	1620 patients planned
Interventions	Surgery + chemotherapy vs surgery
Outcomes	Overall survival
Starting date	March 2009
Contact information	Protocol Chair: David Harpole MD
Notes	Estimated completion date, Jan 2014

DATA AND ANALYSES

Comparison 1. Surgery versus surgery + adjuvant chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	34		Hazard Ratio (95% CI)	Subtotals only
1.1 Platinum + vinca alkaloid/etoposide	9	2404	Hazard Ratio (95% CI)	0.94 [0.84, 1.05]
1.2 Platinum + vinorelbine	4	1304	Hazard Ratio (95% CI)	0.82 [0.70, 0.97]
1.3 Platinum + taxane	1	344	Hazard Ratio (95% CI)	0.77 [0.57, 1.05]
1.4 Other platinum regimens	4	699	Hazard Ratio (95% CI)	0.90 [0.72, 1.13]
1.5 Platinum + vinca alkaloid + tegafur and uracil/tegafur	8	1375	Hazard Ratio (95% CI)	0.79 [0.67, 0.93]
1.6 Tegafur and uracil/tegafur + other agent	1	83	Hazard Ratio (95% CI)	1.79 [1.00, 3.20]
1.7 Tegafur and uracil/tegafur	7	2390	Hazard Ratio (95% CI)	0.76 [0.64, 0.90]

Comparison 2. Surgery + radiotherapy versus surgery + radiotherapy + adjuvant chemotherapy

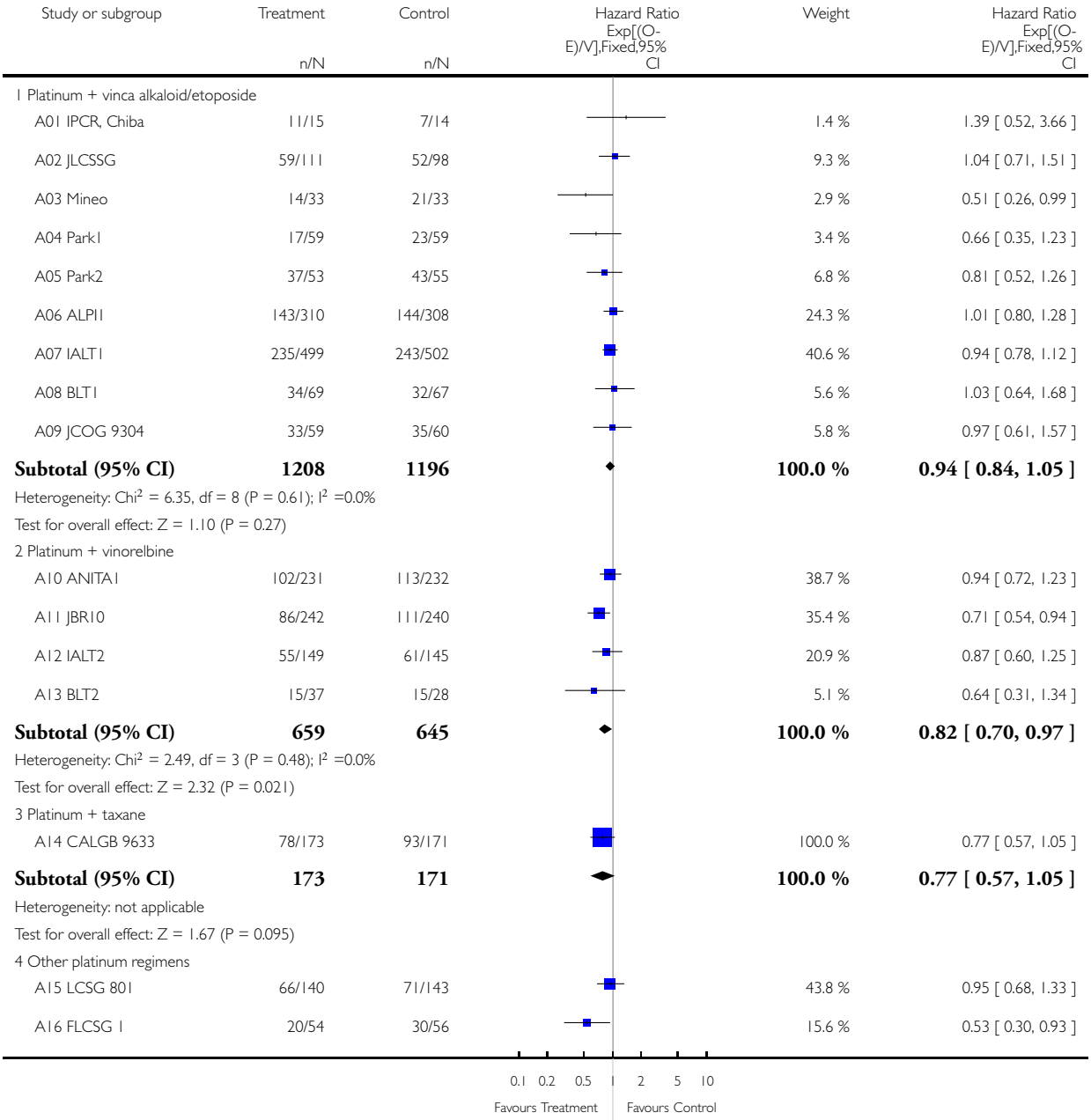
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	13	2660	Hazard Ratio (95% CI)	0.88 [0.81, 0.97]
1.1 Platinum + vinca alkaloid/etoposide	8	1770	Hazard Ratio (95% CI)	0.93 [0.83, 1.03]
1.2 Platinum + vinorelbine	2	583	Hazard Ratio (95% CI)	0.77 [0.63, 0.94]
1.3 Other platinum regimen	2	258	Hazard Ratio (95% CI)	0.85 [0.65, 1.11]
1.4 Antimetabolic agent only	1	49	Hazard Ratio (95% CI)	1.02 [0.45, 2.34]

Analysis 1.1. Comparison 1 Surgery versus surgery + adjuvant chemotherapy, Outcome 1 Survival.

Review: Adjuvant chemotherapy for resected early-stage non-small cell lung cancer

Comparison: 1 Surgery versus surgery + adjuvant chemotherapy

Outcome: 1 Survival



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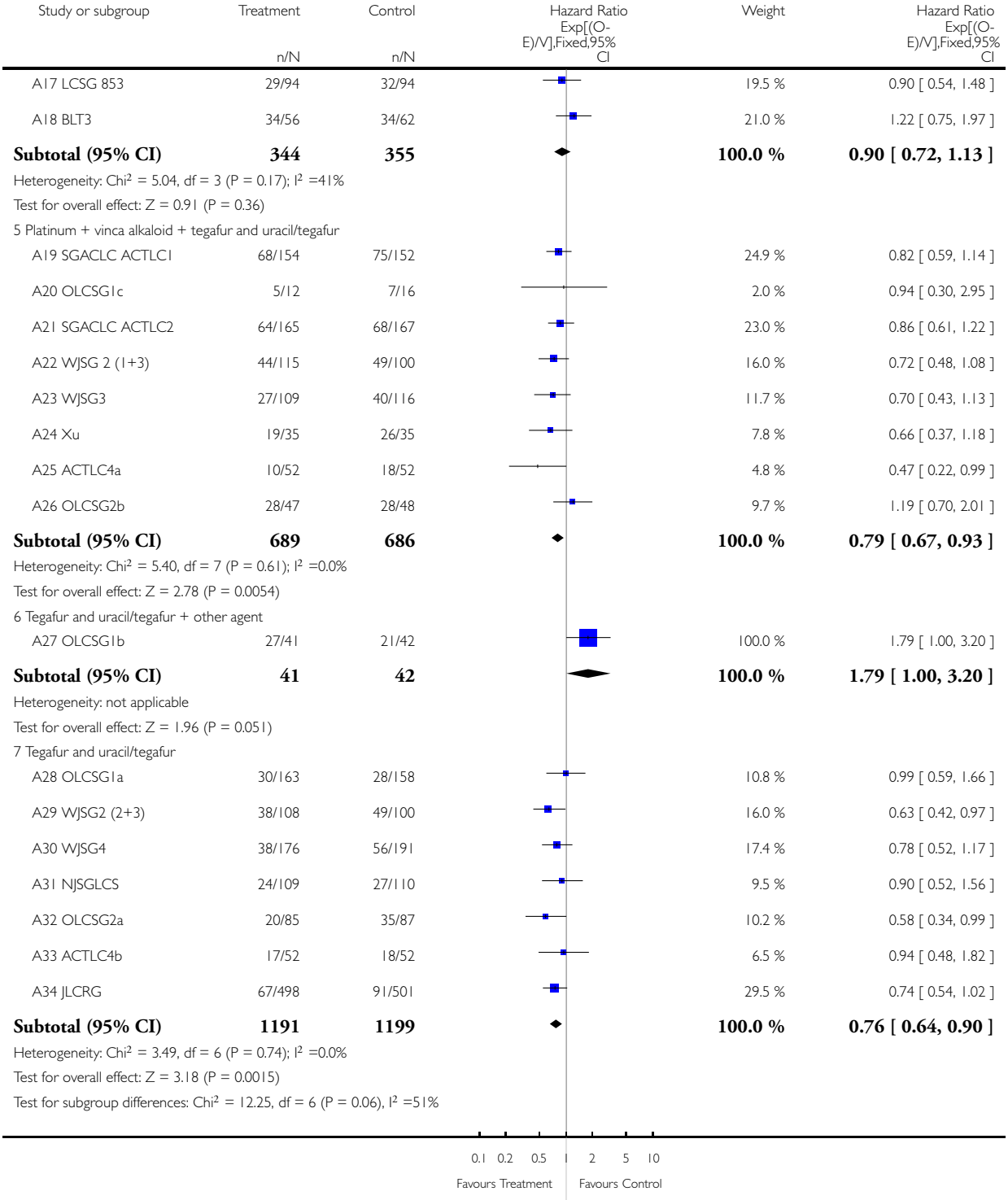


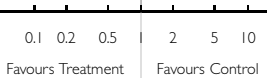
Analysis 2.1. Comparison 2 Surgery + radiotherapy versus surgery + radiotherapy + adjuvant chemotherapy, Outcome 1 Survival.

Review: Adjuvant chemotherapy for resected early-stage non-small cell lung cancer

Comparison: 2 Surgery + radiotherapy versus surgery + radiotherapy + adjuvant chemotherapy

Outcome: 1 Survival

Study or subgroup	Treatment n/N	Control n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
1 Platinum + vinca alkaloid/etoposide					
B01 MSKCC 80-53	34/36	34/36		3.5 %	1.12 [0.69, 1.81]
B02 GETCB 01CB82	125/138	115/129		12.5 %	0.93 [0.72, 1.21]
B03 EORTC 08861	5/10	8/14		0.6 %	1.04 [0.34, 3.26]
B04 MDA DM 87045	15/16	18/18		1.7 %	0.84 [0.42, 1.67]
B05 INT 0115	183/246	186/242		19.5 %	0.96 [0.79, 1.18]
B06 ALPI2	136/238	146/232		14.9 %	0.87 [0.69, 1.10]
B07 IALT3	125/185	133/181		13.6 %	0.89 [0.70, 1.14]
B08 BLT4	15/23	18/26		1.7 %	0.94 [0.47, 1.89]
Subtotal (95% CI)	**892**	**878**		**67.8 %**	**0.93 [0.83, 1.03]**
Heterogeneity: Chi^2 = 1.26, df = 7 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.39 (P = 0.16)					
2 Platinum + vinorelbine					
B09 ANITA2	104/176	139/201		12.8 %	0.70 [0.55, 0.90]
B10 IALT4	59/99	69/107		6.7 %	0.92 [0.65, 1.30]
Subtotal (95% CI)	**275**	**308**		**19.5 %**	**0.77 [0.63, 0.94]**
Heterogeneity: Chi^2 = 1.46, df = 1 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 2.51 (P = 0.012)					
3 Other platinum regimen					
B11 LCSG 791	68/82	75/90		7.5 %	0.85 [0.61, 1.18]
B12 FLCSG 3	34/40	42/46		4.0 %	0.84 [0.54, 1.33]
Subtotal (95% CI)	**122**	**136**		**11.5 %**	**0.85 [0.65, 1.11]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
4 Antimetabolic agent only					
B13 OLCSG1d	13/26	10/23		1.2 %	1.02 [0.45, 2.34]
Subtotal (95% CI)	**26**	**23**		**1.2 %**	**1.02 [0.45, 2.34]**



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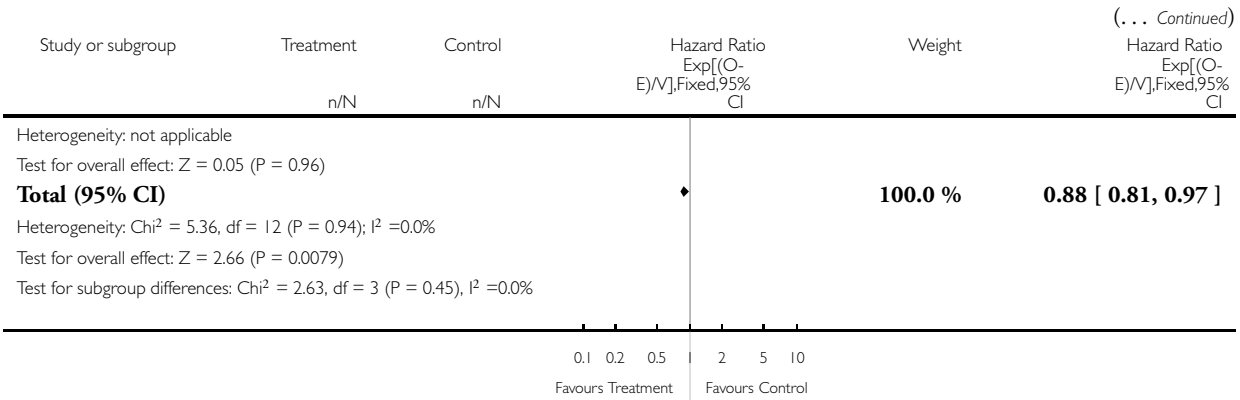

ADDITIONAL TABLES

Table 1. Recent meta-analyses of surgery (+/- radiotherapy) + chemotherapy versus surgery (+/- radiotherapy)

Author	Type of data	Number of trials	Number of patients	Outcome	Hazard Ratio (95% CI)
Hotta 2004	Published data	11*	5716	Survival	0.87 (0.81 to 0.94)
Sedrakyan 2004	Published data	19	7200	Survival	0.87 (0.81 to 0.93)
Berghmans 2005	Published data	17	7644	Survival	0.85 (0.79 to 0.91)
Bria 2005	Published data	11 + 1 meta-analysis	6494	Survival	0.93 (0.89 to 0.95)
Hamada 2005	Individual participant data	6**	2003	Survival	0.74 (0.61 to 0.88)
Pignon 2008	Individual participant data	5†	4584	Survival Event-free survival	0.89 (0.82 to 0.96) 0.84 (0.78 to 0.91)

* Recent trials only
**UFT trials only
† Large (> 300 patients) and recent cisplatin trials only

Table 2. Patient characteristics for trials of surgery + chemotherapy versus surgery and for trials of surgery + radiotherapy + chemotherapy versus surgery + radiotherapy

Characteristic	Surgery + CT* (n = 4305)	Surgery (n = 4142)	Surgery + RT** + CT (n = 1315)	Surgery + RT (n = 1345)
Age (years)				
< 60	1827 (46%)	1669 (44%)	692 (53%)	693 (51%)
60 - 64	898 (17%)	900 (18%)	270 (20%)	292 (22%)
65 - 69	872 (20%)	878 (21%)	253 (19%)	253 (19%)
>= 70	593 (14%)	583 (14%)	100 (8%)	107 (8%)
Unknown	115 (3%)	112 (3%)	-	-
Sex				
Male	2948 (68%)	2876 (69%)	1023 (78%)	1062 (79%)
Female	1238 (29%)	1149 (28%)	291 (22%)	281 (21%)
Unknown	119 (3%)	117 (3%)	1 (< 1%)	2 (< 1%)
Histology				
Adenocarcinoma	2257 (52%)	2158(52%)	499 (38%)	501 (37%)
Squamous	1649 (38%)	1587 (38%)	642 (49%)	655 (49%)
Other	386 (9%)	391 (9%)	172 (13%)	184 (14%)
Unknown	13 (< 1%)	6 (< 1%)	2 (< 1%)	5 (< 1)
Stage				
I	2851 (66%)	2772 (67%)	20 (2%)	14 (1%)
II	806 (19%)	793 (19%)	450 (34%)	473 (35%)
IIIa	586 (14%)	512 (12%)	804 (61%)	801 (60%)
IIIb	31 (< 1%)	42 (1%)	21 (2%)	30 (2%)
Stage III Unspecified	-	-	-	3(<1%)
IV	13 (< 1%)	10 (< 1%)	3 (< 1%)	0 (0%)

Table 2. Patient characteristics for trials of surgery + chemotherapy versus surgery and for trials of surgery + radiotherapy + chemotherapy versus surgery + radiotherapy (*Continued*)

Unknown	18 (< 1%)	13 (< 1%)	17 (1%)	24 (2%)
Performance status†				
Good	3172 (74%)	3022 (73%)	948 (72%)	969 (72%)
Poor	96 (2%)	83 (2%)	81 (6%)	105 (8%)
Unknown	76 (2%)	58 (1%)	22 (2%)	16 (1%)
Not supplied	961 (22%)	979 (24%)	264 (20%)	255 (19%)
Extent of resection				
Complete	4119 (96%)	3951 (95%)	1097 (83%)	1121 (83%)
Incomplete	120 (3%)	123 (3%)	179 (14%)	186 (14%)
Unknown	66 (1%)	68 (2%)	39 (3%)	38 (3%)
Radiotherapy timing				
CT before RT	-	-	941 (72%)	963 (72%)
Concomitant CT + RT	-	-	374 (28%)	382 (28%)

*CT = Chemotherapy
**RT = Radiotherapy
†Good = 0,1 ECOG/WHO or 100 - 70 Karnofsky; Poor > 2 ECOG/OMS or <= 60 Karnofsky

APPENDICES

Appendix 1. MEDLINE Search Strategy

Cochrane Highly Sensitive Search Strategy for identifying RCTs (MEDLINE) (Lefebvre 2008)
1. "randomi*ed controlled trial".pt.
2. controlled clinical trial.pt.
3. "randomi*ed".ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. (animals not (humans and animals)).sh.
11. 9 not 10
Terms specific to lung cancer:
12. exp Lung Neoplasms/
13. exp Carcinoma, Non-Small-Cell Lung/
14. (lung$ adj3 canc$).mp.
15. (lung$ adj3 carcinoma$).mp.
16. (lung$ adj3 tumo?r$).mp.
17. (lung$ adj3 neoplasm$).mp.
18. 12 or 13 or 14 or 15 or 16 or 17
Terms specific to the intervention:
19. exp Drug Therapy/
20. chemotherapy.mp.
21. 19 or 20
22. exp Radiotherapy/
23. radiotherapy.mp.
24. 22 or 23
25. exp General Surgery/
26. surgery.mp.
27. 25 or 26
28. 21 or 24 or 27
29. 11 and 18 and 28

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DECLARATIONS OF INTEREST

There is no known conflict of interest.

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- ARC 2025, France.

NOTES

This review is an update of part of previous review, NSCLC Collaborative Group 2000. This review supercedes the previous review which will not be updated.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Carcinoma, Non-Small-Cell Lung [*drug therapy; mortality; pathology; radiotherapy; *surgery]; Chemotherapy, Adjuvant; Combined Modality Therapy [methods]; Lung Neoplasms [*drug therapy; mortality; pathology; radiotherapy; *surgery]; Randomized Controlled Trials as Topic; Tumor Burden

MeSH check words

Humans